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Nonsteroidal Anti-inflammatory Drugs and Change in Mammographic Density: A Cohort Study Using Pharmacy Records on Over 29,000 Postmenopausal Women

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Abstract

Background—Use of nonsteroidal anti-inflammatory drugs (NSAID) has been associated with a decrease in breast cancer risk, but it is unknown if they also reduce mammographic density, a strong intermediate marker of breast cancer risk.

Methods—We investigated NSAID use and mammographic density in 29,284 postmenopausal women who had two screening mammograms at Group Health in Seattle. We used pharmacy records to classify women as NSAID nonusers, continuers, initiators, or discontinuers based on use between the two mammograms and nine separate prescription and nonprescription NSAID classes. Using unordered polytomous logistic regression methods, we modeled the odds ratio (OR) of staying not dense, decreasing density, or increasing density relative to remaining dense based on Breast Imaging Reporting Data System classification of density.

Results—There was no association with density change from initiation or continuation of NSAIDs. However, both initiators and continuers of any NSAIDs were more likely to stay not dense than stay dense [OR, 1.12; 95% confidence interval (95% CI), 1.04-1.20; OR, 1.25; 95% CI, 1.05-1.49, respectively]. This association with staying not dense for initiators and continuers of any NSAID use was observed primarily among women ages <65 years at first mammogram (OR, 1.24; 95% CI, 1.12-1.36; OR, 1.48; 95% CI, 1.14-1.93, respectively).

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Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Conclusions—Initiation of NSAID use did not reduce mammographic density over the short term. Continuers of NSAID use were more likely to stay not dense compared with nonusers, suggesting that it is plausible that longer-term use of NSAIDs may be needed to reduce density.

Introduction

Nonsteroidal anti-inflammatory drug (NSAID) use has been associated with a reduction in many cancers (1, 2). NSAIDs inhibit cyclooxygenase, which catalyzes the synthesis of prostaglandins; prostaglandin inhibition has reduced tumor formation in animal models (3, 4). Many observational epidemiologic studies of aspirin and other NSAIDs and breast cancer risk have supported a reduction in risk usually in the range of 20% to 40% (1, 5-23), although several prospective observational studies (24-27) as well as prevention trials, like the Women's Health Study, have not (28). The inconsistencies across studies may be explained by real differences in dose and duration of NSAIDs across the studies and/or by reporting biases and residual confounding likely to be present in observational settings.

Despite the large, and growing, literature on NSAIDs and breast cancer risk, little is known regarding the relation between NSAID use and mammographic breast density. Mammographic density, which reflects the amount of epithelial and stromal tissue compared with total breast tissue, is one of the strongest indicators of future breast cancer risk (29-33). Recently, a large study supported that decreases in mammographic density over time are associated with decreases in breast cancer risk (34). Many breast cancer risk factors, including hormone replacement use, parity, and alcohol use, have also been associated with mammographic density (35-44). NSAIDs, through cyclooxygenase inhibition, may affect estrogen biosynthesis. Prostaglandins, like PGE_2, have been shown to increase aromatase gene expression and thereby estrogen production in cultured cells (45) as well as stimulate progesterone synthesis (46). Increase in both progesterone and estrogen may increase mammographic density (47); thus, inhibition of prostaglandin synthesis through NSAIDs may reduce breast density.

We undertook a study to investigate whether NSAID use was associated with changes in mammographic density. We did so by using prospectively collected data from the Group Health pharmacy records of 29,284 women who had mammographic density readings from at least two separate routine mammography screening exams. All mammographic density assessments were conducted blinded to exposure information, and all exposure information was from pharmacy records and not based on individual self-reports.

Materials and Methods

Study Population

Group Health, an integrated group practice in western Washington State with ~550,000 members, has a population-based Breast Cancer Screening Program that women are invited to join at their first mammogram (48, 49). Self-reported demographic and breast cancer risk factor information are gathered by a self-administered questionnaire from women when they join the Breast Cancer Screening Program and at each screening mammogram (49).

We identified 30,834 women who had two routine screening mammograms within 9 to 28 months of each other anytime between 1996 and 2006; if the same women had multiple exams during these years, we selected two exams closest to 18 months apart. We excluded women who reported ever using raloxifene or tamoxifen, women with a history of breast cancer either before or detected at the first screening mammogram, or women who had breast augmentation or reduction reported at either exam. No exclusion criteria were made by race or age but we did exclude women who were premenopausal at either mammogram screening. We further excluded women who had no information on age at menopause or type of menopause or information on other covariates, including body size and hormone replacement use. A total of 29,284 met these criteria and were available for analysis. The study was approved by the institutional review boards of Group Health and Columbia University. A waiver of consent for all women entering the Group Health breast screening clinic to allow for linkage of data and a waiver for Health Insurance Portability and Accountability Act authorization from the institutional review board were obtained.

Categorization of NSAID Use

We searched automated pharmacy records to collect information on aspirin and other NSAID dispensings. We classified aspirin and NSAID use into the following nine categories: aspirin, proprionic acid, indole/indene acids, anthranillic acids, enolic acids, heteroaryl acetic acid, alkones, and two classes of cyclooxygenase inhibitors (Coxib1 and Coxib2). We further categorized NSAID use by nonprescription, prescription, and any NSAID use. Nonprescription NSAID use included aspirin and proprionic acid. Prescription NSAID use included indole/indene acids, anthranillic acids, enolic acids, heteroaryl acetic acid, alkones, and cyclooxygenase inhibitors. Any NSAID use included use of any of the nine classes of NSAIDs.

For each NSAID type, we first described use before the date of the first mammogram by duration of use (total days supplied) in the 10 years before the first mammogram. Duration of use between mammograms was recorded by the total days supply for all dispensings between the two mammograms. The intended duration of each dispensing (and the run out date) was established using automated data on number of pills dispensed. A new run-out date was set with each successive dispensing rather than using cumulative number of pills from all dispensings (50). We used the dispensing information to categorize women as initiators, discontinuers, continued users, or never users of NSAIDs at the two mammograms using information on dispensings before the first mammogram and for the time between both mammograms following groups. Initiators were women who did not use the NSAID at the time of the first mammogram but started before their second mammogram and must have had a dispensing within 6 months of the second mammogram. Continuers were women who had pharmacy dispensings for the entire period between the two mammograms. Discontinuers were women who were dispensed a given class of NSAIDs at the first mammogram but had no dispensings within 6 months before the second mammogram. Nonusers did not have any pharmacy fills for a given class of NSAID within the 6 months before the first and the second mammograms. Individuals who may have initiated one type of NSAID while discontinuing another or continued one type of NSAID while initiating or discontinuing another were defined as “mixed” type and treated as a separate category.

Classification of Mammographic Density

All mammograms completed at Group Health received Breast Imaging Reporting Data System (BI-RADS; ref. 51) breast density measures as part of the clinical interpretation (1, entirely fat; 2, scattered fibroglandular; 3, heterogeneously dense; 4, extremely dense). The reliability of the BI-RADS assessment has ranged from ~0.6 to 0.8 (52-54). The BI-RADS measure has been shown in many studies to be associated with breast cancer risk, and even more recently, changes in BI-RADS categories have been associated with changes in breast cancer risk (34). A description of the reliability and validity of the measure has been added to the methods.

We categorized change in density by comparing responses for the BI-RADS score for the two time points. We created four categories: stayed nondense (women who remain in BI-RADS category 1 or 2 at both exams), stayed dense (women who remain in category 3 or 4 at both exams), increased density (women who increase from category 2 to 3), and decreased density (women who decrease from category 3 to 2; ref. 47). In addition to these primary classifications, we also examined the association between NSAID use and one category change through both continuous and categorical measures (see statistical analysis section below).

Other Risk Factor Data

The Breast Cancer Screening Program questionnaire collects data on established breast cancer risk factors, such as age at menarche, age at menopause, type of menopause, oral contraceptive use, hormone replacement therapy (HRT) use, type and duration of hormone therapy used, age at first birth, parity, benign breast biopsy history, number of previous breast biopsies, race, body mass index (BMI), and date of last mammogram. Self-report information is updated at each mammogram. Our study was designed so each woman's density was compared between two time points. As such, confounders, either measured with error or unmeasured, which do not change with time, will not explain density differences over time. Therefore, in addition to age at the first mammogram, we only included covariates that could have changed between two exams in the multivariable models: hormone therapy, BMI, and time between exams.

Statistical Analysis

We compared characteristics of women by category of any NSAID use (nonuser, initiator, discontinuer, continuer, or mixed type) by age, race, ethnicity, BMI, breast density at first and second mammograms, HRT at first and second mammograms, and days between exams. We then compared the distribution of women by NSAID user type (nonuser, initiator, discontinuer, continuer, or mixed type) by their BI-RADS category on both exams. In addition to univariate statistics, we examined the association between NSAID use and mammographic density by using ordered polytomous logistic regression (55). We modeled three logits compared for women who increased, decreased, and remained nondense and compared them with the reference group of women who remained dense. We considered women who remained dense as the reference group to examine the hypothesis that women who initiated NSAIDS would decrease density relative to those who remained dense.

We examined any NSAID, prescription NSAID, or nonprescription NSAID based on status as nonuser, initiator, discontinuer, continuer, or mixed type user. The exposure reference group was the nonuser category for all classes of NSAIDs. In addition to the age-adjusted models, we examined the following variables that changed between the first and the second mammograms to test whether they confounded the relation between density and NSAID use: HRT, BMI, and time between exams. HRT use was categorized relative to nonusers as initiators, discontinuers, or continuers based on use at the two mammography exams. BMI was examined both as a continuous difference and as a categorical difference (<25, >25) between the two exams. Time between exams was represented as a continuous variable measured in days. In addition to these *a priori* confounders that were based on risk factors that change since the baseline mammogram and are known to effect density, we did supplemental analyses that adjusted for other known risk factors for breast cancer, including family history of breast cancer, parity, age at first birth, and age at menarche. These variables and the *a priori* confounders were only included in the final models if they altered the variable estimates on NSAID use by >10%.

We also examined whether the association between any NSAID use and change in breast density was modified by age at first mammography (≤65, >65), HRT use (ever/never), time between mammograms (≤2, >2 years), and BMI at first mammogram (≤25, >25). In addition to the primary models that categorized density change as described above, we did secondary analysis examining whether our inferences changed when only examining a one-unit change in density through repeated binary logistic models.

Results

Of the 29,284 women, 89% were White, 7% were African American, and 4% were other race. Table 1 summarizes the descriptive statistics by category of any NSAID use (nonusers, initiator, discontinuer, continuer, and mixed). Nonusers of NSAIDs were more likely to be younger, have lower BMI, be never users of HRT, and have dense breast tissue (BI-RADS category 3 or 4). Age at menarche, family history of breast cancer, and age at first birth were similar between nonusers and initiators of NSAIDs; however, mixed users of NSAIDS were more likely to differ from nonusers on these factors. The average time between exams was similar between initiators and nonusers of NSAIDs but was lower for continuers and users of mixed type. Overall, the range for the time between exams was 247 to 881 days.

Table 2 presents a cross-tabulation of breast density at the two exams according to category of any NSAID use. In general, the pattern of density changes was similar across the four categories of NSAID use. For example, 24.8% of NSAID initiators who had heterogeneously dense breasts (category 3 BI-RADS) at the first mammogram decreased density to scattered fibroglandular (category 2 BI-RADS) at the second mammogram compared with 22.1% of nonusers, 28% of discontinuers, 24.3% of continuers, and 26.6% of mixed use category.

Table 3 presents the age-adjusted and multivariable odds ratio (OR)–adjusted findings for all categories of use (initiator, discontinuer, continuer, and mixed) by any NSAID use and separately by nonprescription NSAIDs (aspirin and proprionic acid) and prescription

NSAIDs (the other seven classes). Initiators and continuers of any NSAID were more likely to stay not dense than stay dense [multivariable OR, 1.12; 95% confidence interval (95% CI), 1.04-1.20; multivariable OR, 1.25; 95% CI, 1.05-1.49, respectively]. Point estimates were the same for initiators of nonprescription and prescription NSAIDs for staying not dense compared with staying dense (multivariable OR, 1.11; 95% CI, 1.03-1.20; multivariable OR, 1.11; 95% CI, 0.97-1.26, respectively). Discontinuers of nonprescription NSAIDs were more likely to decrease density compared with nonusers (OR, 1.40; 95% CI, 1.10-1.79) compared with staying dense. There was no association with density change from discontinuation of prescription NSAIDs nor was there an association between continuation of NSAIDs (either prescription or nonprescription) and density change (increase or decrease). However, continuers of nonprescription NSAIDs were more likely to stay not dense compared with those who stayed dense (OR, 1.40; 95% CI, 1.13-1.72). Users in the "mixed" type category of NSAID use included individuals who may have initiated, discontinued, or continued NSAID use within the same period. Mixed users of nonprescription NSAIDs were more likely to increase density, whereas mixed users of prescription NSAIDS were less likely to increase density (OR, 1.64; 95% CI, 1.08-2.48; OR, 0.58; 95% CI, 0.35-0.96, respectively).

We further examined whether the association between any NSAID use and change in mammographic density was modified by age at first mammogram (<65, >65), HRT use (ever, never), time between mammograms (<2, >2 years), and BMI at first mammogram (<25, >25). Only age at first mammogram significantly modified the association (test for multiplicative interaction $P = 0.02$). These findings are presented in Table 4. The overall finding that initiators and continuers of any NSAIDs were more likely to stay not dense compared with staying dense reported in Table 4 was limited to women ages <65 years (OR, 1.24; 95% CI, 1.12-1.36; OR, 1.48; 95% CI, 1.14-1.93 for women ages <65 years compared with OR, 1.02; 95% CI, 0.92-1.14; OR, 1.18; 95% CI, 0.93-1.48 for women ages ≥65 years).

In addition to these primary analyses, we did secondary analyses to evaluate whether a one-unit change in BI-RADS within the category of stayed not dense (category 1 and 2) and stayed dense (category 3 and 4) altered our conclusions. There was no association between each category of any NSAID use (initiation, discontinuation, continuation, and mixed type) and increasing density by a one-unit change in BI-RADS (category 1-2 compared with staying at category 1; 2, to 3 compared with staying at category 2; 3, to 4 compared with staying at category 3; data not shown). There was also no association between each category of any NSAID use and decreasing density by a one-unit change in BI-RADS (category 4 to 3 compared with staying at category 4; 3, to 2 compared with staying at category 3; and category 2 to 1 compared with staying at category 2; data not shown). We further compared individuals who remained at category 2 for both exams with those individuals who remained at category 3 for both exams. Initiation of any NSAID use and continuation of any NSAID use was positively associated with remaining at category 2 compared with those who remained at category 3 (multivariable OR, 1.12; 95% CI, 1.03–1.22; multivariable OR, 1.22; 95% CI, 0.98-1.49, respectively). Thus, if our analyses focused on cross-sectional measures rather than change in density, NSAID use would be associated with overall lower density.

Discussion

Overall, we did not observe a reduction in mammographic breast density from initiation of NSAIDs by class or type of NSAID. Nor did we observe an increase in density from discontinuation of use. We did observe that initiation or continuation of any NSAID use, and nonprescription aspirin in particular, was associated with a 11% to 40% increase chance of staying not dense compared with staying dense. These findings were primarily observed in women ages <65 years.

We investigated density change using the BI-RADS classification where a change in category represents a large change in mammographic density in the range of 25%. Initiation of HRT use has been associated with an increase in breast density using the BI-RADS classification system (47). In our own data, HRT initiation was positively associated with an increase in density relative to staying dense using the categories we described (multivariable OR, 1.59; 95% CI, 1.22-2.06). The increase in mammographic breast density from HRT use has largely been used to argue that estrogen and progesterone levels increase breast density, although direct measures of circulating levels of estradiol have not been associated with higher density and may operate independently of breast density in postmenopausal women (56, 57). Based on the HRT evidence, we hypothesized that NSAIDs may reduce breast density through inhibition of prostaglandins, like PGE_2, which have been shown to increase aromatase gene expression and stimulate progesterone synthesis (46).

To date, change in BI-RADS category, but not smaller within-category changes in density, has been associated with change in breast cancer risk (34). Thus, it is important to continue to understand factors that might relate to large changes in breast density over time. It is entirely plausible that chemoprevention agents such as NSAIDs will result in a within-category change in density rather than a whole category change; however, smaller within-category differences in density have not yet been shown to be related to breast cancer.

Another explanation for the lack of overall association between initiation of NSAID use and density change is the relatively short period covered by this observational study. On average, the two mammograms were from visits just under 2 years apart. Longer-term use of NSAIDs or longer time between mammograms may be needed to observe a more modest effect. Indeed, both continuers and initiators were more likely to stay not dense, but the estimate was slightly higher for continuers, suggesting that longer-term NSAID use may be needed to remain not dense or lower density. We did stratify by time between mammograms and did not observe any large associations for those who had a longer time between mammograms (>2 years) and those who had a shorter time between mammograms (<2 years).

The only other study that has been published examining NSAID use and mammographic density used data from 218 premenopausal women and a separate case-control study of 1,274 women (58). This study by Maskarinec et al. evaluated a single measure of mammographic density using a continuous scale and relied on self-report of NSAIDs. This study did not find any overall association between NSAID use and mammographic density. Among postmenopausal women, long-term NSAID use (>11 years) was associated with a

higher mammographic density. Our study relied on BI-RADS classification and assessment of mammographic change and did not rely on self-reported NSAIDs.

There are many strengths of our large study using data from over 29,000 women. The overall power of the study was extremely high for most comparisons. For example, we had 80% power to detect associations as small as 1.17 between any NSAID and decreasing density. We had 80% power to detect associations as small as 1.18 for nonprescription and 1.3 for prescription NSAIDs. Power for the specific types of prescription NSAIDs was lower; thus, for the primary analyses, we focused on overall, prescription, and nonprescription NSAID rather than specific class. All mammograms were interpreted blinded to any information on exposure to NSAIDs. All exposure information was collected from automated pharmacy records and did rely on individual self-report or recall. It is possible, however, that the pharmacy dispensings were not ingested, and it is likely that nonprescription NSAIDs were purchased outside of Group Health. These misclassification errors likely resulted in a nondifferential measurement error toward the null, which could contribute to our overall lack of association between NSAIDs and density change. The nondifferential measurement error cannot explain the positive association between NSAID use and remaining not dense relative to remaining dense.

Another important strength of our study is that we assessed change in density within individual women. Such a design means that confounders, either measured with error or unmeasured, which do not change with time, cannot account for differences in density. This is important, as regular NSAID users are likely to differ from non-NSAID users in a number of important ways. For example, in our own study, we observed that nonusers of NSAIDs were more likely to be younger, have lower BMI, and never use HRT compared with NSAID users. We were also able to assess factors that may change with time that could have confounded the relation, such as initiation of HRT use or change in BMI. Removing residual confounding in the NSAID and breast cancer risk association is especially important as the only randomized trial of breast cancer risk reported to date did not observe a reduction in risk from low-dose aspirin (28). As a result, some have argued that the consistent association reported in the observational studies, many of which were case-control designs, might be explained by residual confounding and reporting bias. It is true that many of the observational studies of breast cancer risk relied on self-reporting of NSAID use. However, of four studies that used pharmacy or medical records, three reported an inverse association between NSAID use and breast cancer risk (12, 20, 22, 23), suggesting that the inverse association is not limited to studies with self-reported data. Although dose is available in the Group Health automated pharmacy dispensing data, we were less confident that a dose-specific analysis would provide any additional information largely because many of these drugs are over the counter and we had no information on the actual dose women chose to take.

Overall, our study using records from over 29,000 women does not suggest that NSAID initiation over a relatively short period (average, <2 years) can lead to a change in category of mammographic density. We were unable to rule out smaller changes in density from NSAID use or changes in density from longer durations of NSAID use. Both continuers and initiators of NSAIDs were more likely to stay not dense, suggesting that either long-term use

is needed to remain not dense (continuers) or initiation may be correlated with other factors associated with lower density. Our study also reveals the importance of evaluating multiple measures of density over time as a single cross-sectional measure would support the association that ever NSAID use is associated with lower density. Multiple measures reveal a more complex association. Focusing on factors that lead to large changes in density may ultimately prove the greatest benefit for understanding and preventing breast cancer.

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References

1. Jacobs EJ, Thun MJ, Bain EB, Rodriguez C, Henley SJ, Calle EE. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst. 2007; 99:608–15. [PubMed: 17440162]
2. Bardia A, Ebbert JO, Vierkant RA, et al. Association of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs with cancer incidence and mortality. J Natl Cancer Inst. 2007; 99:881–9. [PubMed: 17551148]
3. Carter CA, Milholland RJ, Shea W, Ip MM. Effect of the prostaglandin synthetase inhibitor indomethacin on 7,12-dimethylbenz(a) anthracene-induced mammary tumorigenesis in rats fed different levels of fat. Cancer Res. 1983; 43:3559–62. [PubMed: 6407750]
4. Boolbol SK, Dannenberg AJ, Chadburn A, et al. Cyclooxygenase-2 overexpression and tumor formation are blocked by sulindac in a murine model of familial adenomatous polyposis. Cancer Res. 1996; 56:2556–60. [PubMed: 8653697]
5. Terry MB, Gammon MD, Zhang FF, et al. Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk. JAMA. 2004; 291:2433–40. [PubMed: 15161893]
6. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology. 1994; 5:138–46. [PubMed: 8172988]
7. Rosenberg L. Nonsteroidal anti-inflammatory drugs and cancer. Prev Med. 1995; 24:107–9. [PubMed: 7597007]
8. Harris RE, Kasbari S, Farrar WB. Prospective study of nonsteroidal anti-inflammatory drugs and breast cancer. Oncol Rep. 1999; 6:71–3. [PubMed: 9864404]
9. Harris RE, Namboodiri K, Stellman SD, Wynder EL. Breast cancer and NSAID use: heterogeneity of effect in a case-control study. Prev Med. 1995; 24:119–20. [PubMed: 7597011]
10. Harris RE, Namboodiri KK, Farrar WB. Nonsteroidal antiinflammatory drugs and breast cancer. Epidemiology. 1996; 7:203–5. [PubMed: 8834563]
11. Coogan PF, Rao SR, Rosenberg L, et al. The relationship of nonsteroidal anti-inflammatory drug use to the risk of breast cancer. Prev Med. 1999; 29:72–6. [PubMed: 10446030]
12. Sharpe CR, Collet JP, McNutt M, Belzile E, Boivin JF, Hanley JA. Nested case-control study of the effects of non-steroidal antiinflammatory drugs on breast cancer risk and stage. Br J Cancer. 2000; 83:112–20. [PubMed: 10883678]
13. Cotterchio M, Kreiger N, Sloan M, Steingart A. Nonsteroidal antiinflammatory drug use and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2001; 10:1213–7. [PubMed: 11700271]
14. Johnson TW, Anderson KE, Lazovich D, Folsom AR. Association of aspirin and nonsteroidal anti-inflammatory drug use with breast cancer. Cancer Epidemiol Biomarkers Prev. 2002; 11:1586–91. [PubMed: 12496048]
15. Harris RE, Chlebowski RT, Jackson RD, et al. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. Cancer Res. 2003; 63:6096–101. [PubMed: 14522941]

16. Swede H, Mirand AL, Menezes RJ, Moysich KB. Association of regular aspirin use and breast cancer risk. Oncology. 2005; 68:40–7. [PubMed: 15802928]
17. Slattery ML, Curtin K, Baumgartner R, et al. IL6, aspirin, nonsteroidal anti-inflammatory drugs, and breast cancer risk in women living in the southwestern United States. Cancer Epidemiol Biomarkers Prev. 2007; 16:747–55. [PubMed: 17416766]
18. Gallicchio L, McSorley MA, Newschaffer CJ, et al. Nonsteroidal antiinflammatory drugs, cyclooxygenase polymorphisms, and the risk of developing breast carcinoma among women with benign breast disease. Cancer. 2006; 106:1443–52. [PubMed: 16502408]
19. Harris RE, Beebe-Donk J, Alshafie GA. Reduction in the risk of human breast cancer by selective cyclooxygenase-2 (COX-2) inhibitors. BMC Cancer. 2006; 6:27. [PubMed: 16445867]
20. Rahme E, Ghosn J, Dasgupta K, Rajan R, Hudson M. Association between frequent use of nonsteroidal anti-inflammatory drugs and breast cancer. BMC Cancer. 2005; 5:159. [PubMed: 16343343]
21. Zhang Y, Coogan PF, Palmer JR, Strom BL, Rosenberg L. Use of nonsteroidal antiinflammatory drugs and risk of breast cancer: the Case-Control Surveillance Study revisited. Am J Epidemiol. 2005; 162:165–70. [PubMed: 15972932]
22. Garcia Rodriguez LA, Gonzalez-Perez A. Risk of breast cancer among users of aspirin and other anti-inflammatory drugs. Br J Cancer. 2004; 91:525–9. [PubMed: 15226764]
23. Langman MJ, Cheng KK, Gilman EA, Lancashire RJ. Effect of antiinflammatory drugs on overall risk of common cancer: case-control study in general practice research database. BMJ. 2000; 320:1642–6. [PubMed: 10856067]
24. Paganini-Hill A, Chao A, Ross RK, Henderson BE. Aspirin use and chronic diseases: a cohort study of the elderly. BMJ. 1989; 299:1247–50. [PubMed: 2513898]
25. Egan KM, Stampfer MJ, Giovannucci E, Rosner BA, Colditz GA. Prospective study of regular aspirin use and the risk of breast cancer. J Natl Cancer Inst. 1996; 88:988–93. [PubMed: 8667430]
26. Jacobs EJ, Thun MJ, Connell CJ, et al. Aspirin and other nonsteroidal anti-inflammatory drugs and breast cancer incidence in a large U.S. cohort. Cancer Epidemiol Biomarkers Prev. 2005; 14:261–4. [PubMed: 15668504]
27. Marshall SF, Bernstein L, Anton-Culver H, et al. Nonsteroidal antiinflammatory drug use and breast cancer risk by stage and hormone receptor status. J Natl Cancer Inst. 2005; 97:805–12. [PubMed: 15928301]
28. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA. 2005; 294:47–55. [PubMed: 15998890]
29. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007; 356:227–36. [PubMed: 17229950]
30. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density: a hormonally responsive risk factor for breast cancer. J Br Menopause Soc. 2006; 12:186–93. [PubMed: 17178021]
31. Boyd NF, Rommens JM, Vogt K, et al. Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol. 2005; 6:798–808. [PubMed: 16198986]
32. Pike MC. The role of mammographic density in evaluating changes in breast cancer risk. Gynecol Endocrinol. 2005; 21(Suppl 1):1–5. [PubMed: 16112948]
33. Boyd NF, Byng JW, Jong RA, et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst. 1995; 87:670–5. [PubMed: 7752271]
34. Kerlikowske K, Ichikawa L, Miglioretti DL, et al. Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk. J Natl Cancer Inst. 2007; 99:386–95. [PubMed: 17341730]
35. Oza AM, Boyd NF. Mammographic parenchymal patterns: a marker of breast cancer risk. Epidemiol Rev. 1993; 15:196–208. [PubMed: 8405204]
36. Gram IT, Funkhouser E, Tabar L. Moderate physical activity in relation to mammographic patterns. Cancer Epidemiol Biomarkers Prev. 1999; 8:117–22. [PubMed: 10067808]

37. Nordevang E, Azavedo E, Svane G, Nilsson B, Holm LE. Dietary habits and mammographic patterns in patients with breast cancer. Breast Cancer Res Treat. 1993; 26:207–15. [PubMed: 8251646]
38. Lundstrom E, Wilczek B, von Palffy Z, Soderqvist G, von Schoultz B. Mammographic breast density during hormone replacement therapy: differences according to treatment. Am J Obstet Gynecol. 1999; 181:348–52. [PubMed: 10454681]
39. Boyd NF, Lockwood GA, Martin LJ, et al. Mammographic densities and risk of breast cancer among subjects with a family history of this disease. J Natl Cancer Inst. 1999; 91:1404–8. [PubMed: 10451446]
40. Boyd NF, Lockwood GA, Byng JW, Tritchler DL, Yaffe MJ. Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 1998; 7:1133–44. [PubMed: 9865433]
41. Laya MB, Gallagher JC, Schreiman JS, Larson EB, Watson P, Weinstein L. Effect of postmenopausal hormonal replacement therapy on mammographic density and parenchymal pattern. Radiology. 1995; 196:433–7. [PubMed: 7617857]
42. Bjurstam N, Bjorneld L, Duffy SW, et al. The Gothenburg breast screening trial: first results on mortality, incidence, and mode of detection for women ages 39-49 years at randomization. Cancer. 1997; 80:2091–9. [PubMed: 9392331]
43. Chan SM, Nelson EA, Leung SS, Cheng JC. Bone mineral density and calcium metabolism of Hong Kong Chinese postpartum women—a 1-y longitudinal study. Eur J Clin Nutr. 2005; 59:868–76. [PubMed: 15915158]
44. Greendale GA, Reboussin BA, Sie A, et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. Ann Intern Med. 1999; 130:262–9. [PubMed: 10068383]
45. Zhao Y, Agarwal VR, Mendelson CR, Simpson ER. Estrogen biosynthesis is proximal to a breast tumor is stimulated by PGE2 via cyclic AMP leading to activation of promoter II of the CYP 19 (aromatase) gene. Endocrinology. 1996; 137:5739–42. [PubMed: 8940410]
46. Elvin JA, Yan C, Matzuk MM. Growth differentiation factor-9 stimulates progesterone synthesis in granulose cells via a prostaglandin E2/EP2 receptor pathway. Proc Natl Acad Sci U S A. 2000; 97:10288–93. [PubMed: 10944203]
47. Rutter CM, Mandelson MT, Laya MB, Seger DJ, Taplin S. Changes in breast density associated with initiation, discontinuation, and continuing use of hormone replacement therapy. JAMA. 2001; 285:171–6. [PubMed: 11176809]
48. Taplin SH, Mandelson MT, Anderman C, et al. Mammography diffusion and trends in late-stage breast cancer: evaluating outcomes in a population. Cancer Epidemiol Biomarkers Prev. 1997; 6:625–31. [PubMed: 9264276]
49. Taplin SH, Ichikawa L, Buist DS, Seger D, White E. Evaluating organized breast cancer screening implementation: the prevention of late-stage disease? Cancer Epidemiol Biomarkers Prev. 2004; 13:225–34. [PubMed: 14973097]
50. Buist DS, Newton KM, Miglioretti DL, et al. Hormone therapy prescribing patterns in the United States. Obstet Gynecol. 2004; 104:1042–50. [PubMed: 15516400]
51. American College of Radiology. The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS). 4th ed.. American College of Radiology; Reston (VA): 2003.
52. Kerlikowske K, Grady D, Barclay J, Sickles EA, Ernster V. Effect of age, breast density, and family history on the sensitivity of first screening mammography. JAMA. 1996; 276:33–8. [PubMed: 8667536]
53. Ooms EA, Zonderland HM, Eijkemans MJ, et al. Mammography: interobserver variability in breast density assessment. Breast. 2007; 16:568–76. [PubMed: 18035541]
54. Ciatto S, Houssami N, Apruzzese A, et al. Categorizing breast mammographic density: intra- and interobserver reproducibility of BI-RADS density categories. Breast. 2005; 14:269–75. [PubMed: 16085233]
55. Hosmer, DW.; Lemeshow, S. Applied logistic regression. John Wiley and Sons; New York: 1989.
56. Tamimi RM, Byrne C, Colditz GA, Hankinson SE. Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 2007; 99:1178–87. [PubMed: 17652278]

57. Tamimi RM, Hankinson SE, Colditz GA, Byrne C. Endogenous sex hormone levels and mammographic density among postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2005; 14:2641–7. [PubMed: 16284390]

58. Maskarinec G, Urano Y, Gill J, Kolonel LN. Nonsteroidal antiinflammatory drugs (NSAIDs) and mammographic density. Breast Cancer Res Treat. 2007 Online only [epub ahead of print] 2007 Nov 29; 1-7.

Table 1
Characteristics of postmenopausal women by NSAID use, Group Health, 1996-2006

Characteristics	Nonuser (*n* = 20,653), %	Initiator (*n* = 5,978), %	Discontinuer (*n* = 1,156), %	Continuer (*n* = 838), %	Mixed (*n* = 659), %	*P* *
% Women in each category	70.5	20.4	4.0	2.9	2.2	
Age at first mammogram (y)						
≤49	8.5	7.1	8.1	4.4	6.8	<0.0001
50-59	38.3	30.4	33.3	24.4	26.6	
60-69	28.9	27.9	29.0	27.9	28.1	
70-79	18.9	26.9	23.6	32.7	30.2	
80-98	5.4	7.7	6.0	10.6	8.3	
Age at second mammogram (y)						
≤49	5.3	4.4	6.0	2.8	4.4	<0.0001
50-59	35.3	27.8	30.2	22.1	25.0	
60-69	30.5	28.4	29.5	25.9	26.4	
70-79	21.4	28.2	25.2	34.0	31.9	
80-100	7.5	11.2	9.1	15.2	12.3	
Race						
White	89.1	89.3	88.1	90.1	89.8	0.056
Black	6.9	6.9	7.0	5.6	5.3	
American Indian/Alaska Native	2.1	2.3	3.0	2.9	3.3	
Asian/Hawaiian/Pacific Islander	1.5	1.2	1.6	1.2	0.8	
Unknown	0.4	0.3	0.3	0.2	0.8	
Ethnicity						
Hispanic	3.3	3.9	4.2	3.1	4.2	0.15
Not Hispanic	96.3	95.7	95.2	96.2	95.0	
Unknown	0.4	0.4	0.6	0.7	0.8	
BMI (at first mammogram)						
<25	42.7	34.3	36.0	29.6	25.5	<0.0001
25-30	30.5	32.2	30.5	31.6	30.3	
>30	22.8	29.0	29.8	34.4	38.1	
Unknown	4.0	4.5	3.6	4.4	6.1	
BI-RADS category at first mammogram						
Entirely fat (1)	9.3	11.2	9.2	13.8	10.6	<0.0001
Scattered fibroglandular (2)	43.8	47.6	47.2	50.1	51.0	
Heterogeneously dense (3)	39.5	35.5	38.0	31.9	33.1	
Extremely dense (4)	7.4	5.7	5.6	4.2	5.3	
BI-RADS category at second mammogram						
Entirely fat (1)	7.6	9.5	7.4	10.7	11.4	<0.0001
Scattered fibroglandular (2)	43.1	46.9	48.9	49.6	46.4	
Heterogeneously dense (3)	42.5	38.4	39.5	35.6	37.5	

Characteristics	Nonuser (*n* = 20,653), %	Initiator (*n* = 5,978), %	Discontinuer (*n* = 1,156), %	Continuer (*n* = 838), %	Mixed (*n* = 659), %	*P* *
Extremely dense (4)	6.8	5.2	4.2	4.1	4.7	
HRT use						
Nonuser	26.6	23.1	23.3	21.2	19.6	<0.0001
Initiator	1.9	2.3	1.5	2.1	1.5	
Discontinuer	31.0	30.8	32.4	31.2	30.8	
Continuer	40.3	43.6	42.6	45.0	47.5	
Unknown	0.2	0.2	0.2	0.5	0.6	
Days between exams						
Mean	634.9	632.3	639.1	613.3	619.3	<0.0001
SD	130.5	125.7	128.5	137.8	135.7	
Median	676	670	674	661	671	
Age at menarche (y)						
Never	0.3	0.4	0.4	0.7	0.5	<0.0001
<11	5.6	6.1	7.0	8.9	6.4	
11-14	72.2	73.5	70.0	73.4	77.2	
≥15	10.5	10.8	12.0	9.2	8.0	
Unknown	11.4	9.2	10.6	7.8	7.9	
Family history						
No family history	58.7	60.7	57.5	55.5	57.4	0.0004
First-degree relative	17.8	17.7	19.9	22.1	19.9	
Second-degree relative	14.3	14.1	13.8	12.8	13.8	
Unknown	9.2	7.5	8.8	9.6	8.9	
Age at first birth (y)						
Not parous	15.1	13.1	13.4	10.9	12.8	<0.0001
≤19	16.6	20.1	19.8	21.7	21.8	
20-24	37.7	37.8	39.4	39.3	41.7	
25-29	19.1	18.2	17.6	18.4	16.7	
≥30	9.5	9.0	7.5	7.0	5.5	
Unknown	2.0	1.8	2.3	2.7	1.5	

* *P* values calculated from χ^2 tests of independence between NSAID use category and each calculated for categorical characteristics and from ANOVA for continuous variables.

Table 2

Cross-tabulation of women in each BI-RADS density category at first mammogram compared with value at second mammogram (row percent); Group Health, 1996-2006

Any NSAID use and BI-RADS density category at first mammogram	BI-RADS density category at second mammogram			
	Entirely fat, *n* (%)	Scattered fibroglandular, *n* (%)	Heterogeneously dense, *n* (%)	Extremely dense, *n* (%)
Nonuser				
Entirely fat	869 (45.4)	972 (50.8)	67 (3.5)	6 (0.3)
Scattered fibroglandular	676 (7.5)	6,077 (67.2)	2,238 (24.7)	55 (0.6)
Heterogeneously dense	35 (0.4)	1,800 (22.1)	5,721 (70.0)	614 (7.5)
Extremely dense	2 (0.1)	45 (3.0)	747 (49.0)	729 (47.9)
Initiator				
Entirely fat	314 (46.8)	332 (49.5)	24 (3.6)	<5 (0.1)
Scattered fibroglandular	240 (8.4)	1,943 (68.3)	646 (22.7)	16 (0.6)
Heterogeneously dense	12 (0.5)	526 (24.8)	1,439 (67.8)	146 (6.9)
Extremely dense	0 (0.0)	<5 (0.9)	185 (54.6)	151 (44.5)
Discontinuer				
Entirely fat	49 (46.2)	54 (51.0)	< 5 (2.8)	0 (0.0)
Scattered fibroglandular	37 (6.8)	386 (70.7)	119 (21.8)	<5 (0.7)
Heterogeneously dense	0 (0.0)	123 (28.0)	295 (67.2)	21 (4.8)
Extremely dense	0 (0.0)	<5 (3.1)	39 (60.0)	24 (36.9)
Continuer				
Entirely fat	51 (44.0)	63 (54.3)	<5 (1.7)	0 (0.0)
Scattered fibroglandular	38 (9.1)	287 (68.3)	95 (22.6)	0 (0.0)
Heterogeneously dense	<5 (0.4)	65 (24.3)	183 (68.6)	18 (6.7)
Extremely dense	0 (0.0)	<5 (2.9)	18 (51.4)	16 (45.7)
Mixed				
Entirely fat	41 (58.6)	29 (41.4)	0 (0.0)	0 (0.0)
Scattered fibroglandular	33 (9.8)	219 (65.2)	83 (24.7)	<5 (0.3)
Heterogeneously dense	<5 (0.5)	58 (26.6)	149 (68.3)	10 (4.6)
Extremely dense	0 (0.0)	0 (0.0)	15 (42.9)	20 (57.1)

Table 3

Association between type of NSAIDS and change in mammographic density between two screening mammograms, Group Health, 1996-2006

	Stay dense	Increase			Decrease			Stay not dense		
	n	*n*	OR (95% CI)*	OR (95% CI)†	*n*	OR (95% CI)*	OR (95% CI)†	*n*	OR (95% CI)*	OR (95% CI)†
Nonuser	7,811	2,366	1.00	1.00	1,882	1.00	1.00	8,594	1.00	1.00
Initiators										
Any NSAID	1,921	687	1.13 (1.02-1.25)	1.03 (0.93-1.14)	541	1.14 (1.02-1.27)	1.09 (0.97-1.21)	2,829	1.26 (1.18-1.34)	1.12 (1.04-1.20)
Nonprescription	1,573	576	1.14 (1.02-1.26)	1.05 (0.94-1.17)	449	1.14 (1.01-1.28)	1.11 (0.98-1.25)	2,331	1.22 (1.13-1.31)	1.11 (1.03-1.20)
Prescription	470	171	1.15 (0.96-1.38)	1.03 (0.85-1.24)	139	1.18 (0.97-1.43)	1.08 (0.88-1.32)	725	1.30 (1.15-1.46)	1.11 (0.97-1.26)
Discontinuers										
Any NSAID	379	126	1.07 (0.87-1.32)	1.00 (0.81-1.23)	125	1.35 (1.10-1.67)	1.24 (1.00-1.54)	526	1.22 (1.07-1.40)	1.08 (0.93-1.25)
Nonprescription	279	97	1.14 (0.90-1.44)	1.08 (0.85-1.38)	100	1.48 (1.17-1.87)	1.40 (1.10-1.79)	384	1.21 (1.03-1.42)	1.12 (0.94-1.32)
Prescription	109	31	0.91 (0.61-1.36)	0.77 (0.51-1.15)	29	1.05 (0.70-1.59)	0.88 (0.57-1.35)	155	1.22 (0.95-1.57)	0.96 (0.74-1.25)
Continuers										
Any NSAID	235	97	1.25 (0.98-1.58)	1.09 (0.85-1.41)	67	1.13 (0.85-1.49)	1.02 (0.76-1.35)	439	1.50 (1.27-1.76)	1.25 (1.05-1.49)
Nonprescription	160	65	1.21 (0.90-1.62)	1.10 (0.81-1.48)	51	1.25 (0.91-1.73)	1.19 (0.85-1.65)	320	1.56 (1.28-1.89)	1.40 (1.13-1.72)
Prescription	78	33	1.33 (0.88-2.00)	1.10 (0.72-1.66)	18	0.93 (0.56-1.56)	0.72 (0.42-1.24)	120	1.29 (0.97-1.72)	0.93 (0.69-1.27)
Mixed type‡										
Any NSAID	194	84	1.35 (1.04-1.75)	1.07 (0.81-1.41)	59	1.22 (0.91-1.64)	1.03 (0.75-1.40)	322	1.39 (1.16-1.67)	1.08 (0.89-1.32)
Nonprescription	170	82	1.94 (1.31-2.87)	1.64 (1.08-2.48)	53	1.36 (0.85-2.18)	1.11 (0.67-1.83)	297	1.24 (0.92-1.67)	1.06 (0.77-1.46)
Prescription	134	50	0.66 (0.41-1.06)	0.58 (0.35-0.96)	38	0.88 (0.51-1.53)	0.88 (0.50-1.57)	238	1.26 (0.90-1.76)	1.07 (0.75-1.54)

*Adjusted for age at first mammogram.

†Adjusted for age at first mammogram, BMI at first mammogram, HRT use, and time between the two mammograms.

‡Mixed-type includes individuals who may have initiated one type of NSAID while discontinuing another or continued one type of NSAID while initiating or discontinuing another.

Table 4

Association between any NSAID use and change in mammographic density between two screening mammograms* stratified by age at first mammogram, Group Health, 1996-2006

	<65 y			≥65 y		
	Increase vs stay dense, OR (95% CI)*	Decrease vs stay dense, OR (95% CI)*	Stay not dense vs stay dense, OR (95% CI)*	Increase vs stay dense, OR (95% CI)*	Decrease vs stay dense, OR (95% CI)*	Stay not dense vs stay dense, OR (95% CI)*
Nonuser	1.00	1.00	1.00	1.00	1.00	1.00
Initiator	1.04 (0.90-1.19)	1.12 (0.96-1.30)	1.24 (1.12-1.36)	1.05 (0.90-1.22)	1.06 (0.89-1.25)	1.02 (0.92-1.14)
Discontinuer	0.93 (0.70-1.23)	1.09 (0.82-1.45)	1.00 (0.83-1.22)	1.14 (0.82-1.59)	1.51 (1.08-2.11)	1.22 (0.97-1.54)
Continuer	1.23 (0.85-1.80)	1.07 (0.69-1.65)	1.48 (1.14-1.93)	1.09 (0.78-1.51)	1.01 (0.69-1.48)	1.18 (0.93-1.48)
Mixed	1.30 (0.88-1.92)	1.38 (0.91-2.09)	1.29 (0.97-1.71)	0.96 (0.65-1.41)	0.75 (0.46-1.21)	0.99 (0.75-1.30)

*Adjusted for BMI at first mammogram, HRT use, and time between the two mammograms.